Please amend the claims as follows:

3. (Amended) A non-naturally occurring IA protein comprising an amino acid substitution, wherein said amino acid substitution is selected from B4-Y and B4-F.

7. (Amended) A non-naturally occurring IA protein, wherein said IA protein comprises a substitution selected from the group of B5-F, B5-W, B14-F, B14-W, B14-Y, and B14-I.

8. (Amended) A non-naturally occurring IA protein, wherein said IA protein comprises at least 2 amino acid substitutions from the A-chain and at least 5 amino acid substitutions from the B-chain at positions selected from the group consisting of positions A1, A10, A16, A17, A19, B1, B2, B4, B8, B11, B12, B14, B25, B26, B27 and B28.

10. (Amended) A non-naturally occurring IA protein, wherein said IA protein comprises an amino acid sequence selected from the group of amino acid sequences shown in Figure 3A, Figure 3B, Figure 3C, Figure 3D, Figure 3E, Figure 3F, Figure 3G, Figure 4A, Figure 4B, Figure 4C, Figure 4D, Figure 4E, Figure 4F, Figure 4G, Figure 5A, Figure 5B, and Figure 5C.

11. (Amended) A recombinant nucleic acid encoding the non-naturally occurring IA protein of claim 10.

17. (Amended) A pharmaceutical composition comprising an IA protein according to claim 10 and a pharmaceutical carrier.

Claim Objections:

Claim 3 has been amended to correct the typographical error in duplicating "B7-Y."

REMARKS

Claims 1-17 and 22-29 are pending in the instant application. Claims 23-29 have been withdrawn from consideration. Applicants respectfully reserve the right to pursue claims of similar scope and subject matter in the future. Claims 1, 2, and 4-6 have been canceled without prejudice or disclaimer.

Claim 3 has been amended to independent form. The claim now recites "said amino acid substitution is selected from B4-Y and B4-F," instead of "the group of A7-S, A7-E, B2-E, B2-T, B4-Y, B7-Y, B4-F, B7-Y, B7-E, and B7-D," Further, the claim recites "comprising an amino acid substitution," to clarify the substitution. Support for the amendment to the claim language may be found in original Claim 3.

Claim 7 has been amended to independent form. Support for the amendment may be found in original claim 7.

Claim 8 has been amended to recite " at least 2 amino acid substitutions from the A-chain and at least 5 amino acid substitutions from the B-chain," instead of "At least 5 substitutions." Support for this amendment may be found in original claim 8 and in the Specification on page 6, lines 6-7; page 22, lines 9-11; page 23, lines 1-2; page 29, lines 18-20; page 30, lines 9-13; page 35, lines 18-25; page 36, lines 10-12; and page 36, lines 25-27.

Claim 10 has been amended to independent form. Support for the amendment may be found in original claim 10.

Claims 11 and 17 have been amended to recite "non-naturally occurring IA protein of claim 10," instead of "non-naturally occurring IA protein of claim 1 or 10." Claim 1 is canceled in this Amendment.

Claim Rejections – 35 USC §112, First Paragraph

Claims 1-17 and 22 are rejected under 35 USC §112, first paragraph because the specification, while being enabling for proteins which bind the insulin receptor and have an activity of insulin, does not reasonably provide enablement for proteins which bind to a cell which comprises an insulin receptor.

Claims 1, 2, and 4-6 have been canceled making the above-stated rejection moot.

Claims 1-17 and 22 are rejected under 35 USC §112, first paragraph because the instant claims are based on a computer method of determining likely amino acid substitutions which would result in functional proteins with altered biological activity compared to the native protein. Applicants respectfully disagree because the underlying computer method for determining the amino acid substitutions has previously been tested and demonstrated predictive results. Furthermore, the application provides guidance about how substitutions may be chosen, which will result in functional variants having the desired property. See for example Specification at page 15, lines 14-26; page 27, lines 18-32; page 29, lines 21-23; page 35, lines 18-25; page 36, lines 10-12; and page 36, lines 25-27.

With respect to claims 3, 7-17, and 22, in support of Applicants' statement of predictability, attached hereto, for the Examiner's convenience, are publications, which demonstrate that variant proteins

produced by the disclosed method are active for a desired property. The following publications are marked as "Exhibits" and attached hereto.

The following publications were cited in the Information Disclosure Statement filed December 15, 2000, however have been attached herewith for the Examiner's convenience.

1) Dahiyat, Bassil I. and Stephen L. Mayo, Protein design automation, Protein Science (1996), 5:895-903. (Exhibit A)

2) Dahiyat, Bassil I. and Stephen L. Mayo, De Novo Protein Design: Fully Automated Sequence Selection, Science, 3 October 1997, Volume 278, pp. 82-87. (Exhibit B)

The following publications are provided to support the Applicants' assertion that the variants generated by the underlying computational method are predictable for the desired property:

1) Luo, et al., Development of a cytokine analog with enhanced stability using computational ultrahigh throughput screening, Protein Science, (2002), 11:1218-1226. (Exhibit C)

2) DeGrado, William F., Proteins from Scratch, Science, 3 October 1997, Volume 278, pp. 80-81. (Exhibit D)

3) Filikov, et al., Computational stabilization of human growth hormone, Protein Science (2002), 11:1452-1461. (Exhibit E)

Claim Rejections – 35 USC §102(b)

Claims 1-6, 8, 11-17 have been rejected as being anticipated by U.S. Patent No. 5,618,913 to Brange et al. Brange discloses amino acid substitutions at positions 1, 2, 5, 9, 10, 12, 14, 16-18, 20, and 26-28 of the B-chain and 8-10, 13 and 21 of the A-chain of human insulin as recited in Claim 12 (col. 35) of the Brange patent.

Claims 1, 2, and 4-6 have been canceled by this Amendment making the rejection of these claims moot. With respect to claims 8, and 11-17, Applicants respectfully submit Brange does not anticipate the pending claims for the following reasons. The amino acid substitutions of claim 8 are selected from positions 1, 2, 4, 8, 11, 12, 14, 25, 26, 27, and 28 of the B chain and positions 1, 10, 16, 17, and 19 of the A chain. The present invention claims at least 2 amino acid substitutions from the A-chain and at least 5 amino acid substitutions from the B-chain, thereby distinguishing the present invention from Brange. Additionally, the specific amino acid substitutions in the present invention are distinguishable from those made by Brange. Since Brange does not teach or suggest all of the elements in this claim, the present claims are not anticipated.

In light of the above-arguments, Applicants respectfully request the withdrawal of the rejection of claims 8 and 11-17.

Claims 1 and 5 have been canceled in this Amendment. Therefore, the claim rejections in light of Nakagawa et al. (J. Biol. Chem. 261(16): 7332-7341, 1986) are made moot. Claim 17 has been amended to depend only from Claim 10. Applicants respectfully request the withdrawal of the rejection.

Claims 1 and 5 have been canceled. Therefore, the claim rejection in light of Mirmira et al. (J. Biol. Chem. 266(3): 1428-1436, 1991) is made moot. Applicants respectfully request the withdrawal of the rejection.

Claims 1, 2, 5, and 6 have been canceled making the rejection in light of Marki et al. (Hoppe-Seylers Xeitschrift fur Physiologische Chemie 360(11): 1619-1632, 1979) moot.

Claim 17, now depends from Claim 10. Therefore, Marki et al. does not anticipate Claim 17. Applicants respectfully request the withdrawal of the rejection.

Claims 1, 2, and 5 have been canceled making the rejection in light of Kristensen et al. (J. Biol. Chem 272(20): 12978-12983, 1997) moot. Claims 11-17 have been amended to depend from Claim 10. In light of the amendment to the claims, Applicants respectfully request the withdrawal of the rejection.

In light of the foregoing arguments, Applicants respectfully request the withdrawal of the prior art rejections of the claims.

The Applicants submit that in light of the above-amendment and argument, the claims are now in condition for allowance and an early notification of such is respectfully solicited. Attached hereto is a marked-up version of the changes made to the Specification and Claims by the "Amendment". The attached page is captioned **"Version with markings to show changes made."** Please direct any calls in connection with this application to the undersigned at (626) 737-8019.

Dated: March 28, 2003
111 W. Lemon Avenue
Monrovia, California 91016
Tel: (626) 737-8019; Fax: (626) 256-3562

Respectfully submitted,

By: _____
Joyce L. Morrison, Reg. No. 31,902

VERSION TO SHOW CHANGES MADE

In the Specification (Abstract):

The invention relates to [novel] insulin activity (IA) proteins and nucleic acids. The invention further relates to the use of the IA proteins in the treatment of insulin related disorders such as type1 diabetes and type 2 diabetes.

In the Claims:

3. (Amended) A non-naturally occurring IA protein [according to claim 2] comprising an amino acid substitution, wherein said amino acid substitution is selected from [the group of A7-S, A7-E, B2-E, B2-T, B4-Y, B7-Y, B4-F, B7-Y, B7-E, and B7-D] B4-Y and B4-F.

7. (Amended) [The] A non-naturally occurring IA protein [according to claim 6], wherein said IA protein comprises a substitution selected from the group of B5-F, B5-W, B14-F, B14-W, B14-Y, and B14-I.

8. (Amended) [The] A non-naturally occurring IA protein [according to claim 1], wherein said IA protein comprises [At] at least 2 amino acid substitutions from the A-chain and at least 5 amino acid substitutions from the B-chain at positions selected from the group consisting of positions A1, A10, A16, A17, A19, B1, B2, B4, B8, B11, B12, B14, B25, B26, B27 and B28.

10. (Amended) [The] A non-naturally occurring IA protein, [according to claim 1] wherein said IA protein comprises an amino acid sequence selected from the group of amino acid sequences shown in Figure 3A, Figure 3B, Figure 3C, Figure 3D, Figure 3E, Figure 3F, Figure 3G, Figure 4A, Figure 4B, Figure4C, Figure 4D, Figure 4E, Figure 4F, Figure 4G, Figure 5A, Figure 5B, and Figure 5C.

11. (Amended) A recombinant nucleic acid encoding the non-naturally occurring IA protein of claim [1 or] 10.

17. (Amended) A pharmaceutical composition comprising an IA protein according to claim [1 or] 10 and a pharmaceutical carrier.

PENDING CLAIMS

3. (Amended) A non-naturally occurring IA protein comprising an amino acid substitution, wherein said substitution is selected from B4-Y and B4-F.

7. (Amended) A non-naturally occurring IA protein, wherein said IA protein comprises a substitution selected from the group of B5-F, B5-W, B14-F, B14-W, B14-Y, and B14-I.

8. (Amended) A non-naturally occurring IA protein, wherein said IA protein comprises at least 2 amino acid substitutions from the A-chain and at least 5 amino acid substitutions from the B-chain at positions selected from the group consisting of positions A1, A10, A16, A17, A19, B1, B2, B4, B8, B11, B12, B14, B25, B26, B27 and B28.

9. The non-naturally occurring IA protein according to claim 8, wherein said substitutions are selected from the group of substitutions consisting of A1-N, A10-Q, A16-Y, A17-Y, A19-F, B1-D, B2-K, B4-F, B8-L, B11-I, B12-R, B14-W, B25-N, B26-F, B27-D, and B28-N.

10. (Amended) A non-naturally occurring IA protein, wherein said IA protein comprises an amino acid sequence selected from the group of amino acid sequences shown in Figure 3A, Figure 3B, Figure 3C, Figure 3D, Figure 3E, Figure 3F, Figure 3G, Figure 4A, Figure 4B, Figure4C, Figure 4D, Figure 4E, Figure 4F, Figure 4G, Figure 5A, Figure 5B, and Figure 5C.

11. (Amended) A recombinant nucleic acid encoding the non-naturally occurring IA protein of claim 10.

12. An expression vector comprising the recombinant nucleic acid of claim 11.

13. A host cell comprising the recombinant nucleic acid of claim 11.

14. A host cell comprising the expression vector of claim 12.

15. A method of producing a non-naturally occurring IA protein comprising culturing the host cell of claim 13 under conditions suitable for expression of said nucleic acid.

16. The method according to claim 15 further comprising recovering said IA protein.

17. (Amended) A pharmaceutical composition comprising an IA protein according to claim 10 and a pharmaceutical carrier.

22. A non-naturally occurring IA protein according to claim 10 wherein said IA protein comprises the amino acid sequence shown in Figure 3A (SEQ ID NO: 7).